Submission by Philip Morris U.S.A.

to

The National Toxicology Program

- Appendix 8 -

Section on Carcinogenesis from
Philip Morris U.S.A. Comments on
Health Effects of Exposure to Environmental Tobacco Smoke
Final Draft for Scientific, Public and SRP Review
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
May 5, 1997

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COMMENTS ON:

Health Effects of Exposure to Environmental Tobacco Smoke

Final Draft for Scientific, Public and SRP Review

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PHILIP MORRIS U.S.A.

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COMMENTS ON CHAPTER 7 -- CARCINOGENIC EFFECTS

Summary Overview

Based on Chapter 7, "Carcinogenic Effects," OEHHA contends that (1) the data support a causal relationship between ETS exposure and lung cancer, (2) the data support a causal relationship between ETS exposure and cancer of the nasal sinus and (3) the data are "suggestive" of a causal relationship between ETS exposure and cervical cancer. Philip Morris herein provides comments on those three conclusions. Given the limited time made available for public comments, Philip Morris has not been able to address in detail the other cancer endpoints discussed by OEHHA; this does not mean that the Company endorses OEHHA's conclusions or the reasoning described therein, or that Philip Morris believes that OEHHA's review is complete, impartial, or appropriate. For instance, Philip Morris notes that OEHHA has apparently not considered a number of potentially relevant references that could contribute to its discussion of non-lung cancers; thus, the review in Chapter 7 is incomplete on this basis alone. A list of those references is provided as **Attachment A** to this comment.

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Section 7.2 -- ETS and Lung Cancer

Appendix A of the Final Draft purports to be a "Summary of Public Comments and Responses" received on previously released draft chapters of the document. Pages A-2 and A-3 are described as a "List of Those Commenting"; however, this list is incomplete. In particular, the Comment of Philip Morris U.S.A. on the January 1996 External Review Draft, *Carcinogenic Effects of Exposure to Environmental Tobacco Smoke -- Excerpt: ETS and Lung Cancer*, is not included on the list. In so omitting the Comment of Philip Morris, OEHHA has failed to respond to the many issues raised therein, as it is required to do. Moreover, the essence of the discussion on lung cancer in the Final Draft is unchanged from the January 1996 External Review Draft. Therefore, the Comment already submitted by Philip Morris on the lung cancer claims made by OEHHA is still relevant. That Comment is resubmitted as **Attachment B** to this submission.

In the Comment on lung cancer already submitted by Philip Morris, a number of articles overlooked by OEHHA in its previous draft were referenced; however, OEHHA has failed to incorporate most of those references into the Final Draft document. **Attachment C** to this Section of this Comment lists those articles. It is incumbent upon OEHHA to address the important issues raised by these articles.

In the year since Philip Morris submitted the Comment that OEHHA ignored, additional relevant literature has accumulated in the area of ETS exposure and lung cancer. **Attachment D** to this Comment lists new lung cancer literature, which raises a number of important

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issues relevant to OEHHA's claims. OEHHA should review this literature and incorporate it into the ETS assessment.

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Section 7.3.1 -- Nasal Sinus Cancer

OEHHA Claim: Nasal sinus cancer is listed in Table ES.1 (p. ES-2) under "effects ***causally*** associated with ETS exposure." [emphasis added]

Response:

- Nowhere does OEHHA indicate how it reached a conclusion of "causality." In fact, OEHHA's statements in the text of the document do not even mention a causal relationship.

- The reader of the OEHHA document is led to assume that the conclusion of "causality" is scientifically justified -- because it appears in the Executive Summary of the document -- when, in actuality, OEHHA provides ***no*** rationale at all for such a conclusion, and when the Executive Summary states a conclusion different from the conclusions stated in the text of the document.

- In the text, OEHHA states: "Of the studies examining the effect of ETS exposure on nasal sinus cancers, all three show consistent associations, presenting strong evidence that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults" (p. ES-7) and "Existing studies consistently show a significant positive association between exposure to ETS and nasal sinus cancer in nonsmokers. The results have been observed in studies conducted in eastern and western countries, in males and females, in cohort and case-control study designs, and with some adjustment for possible confounders." (p. 7-28)

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- OEHHA should formally indicate how it reached the determination of causality that warranted the inclusion of nasal sinus cancer in Table ES.1.

OEHHA Claim: "Active smoking is firmly established as a causal factor for cancers of the . . . nasal sinus cavity." (p. 7-26)

Response:

- No references are provided for this contention. However, the 1982 and 1989 Surgeon General's reports and the 1986 IARC Monograph (No. 38), cited elsewhere in the chapter by OEHHA, do not even mention nasal sinus cancer in their discussions of cancers purportedly associated with active smoking.

OEHHA Claim: "There are some data on the role of ETS for other cancer sites. including cancers of nasal sinus cavity . . ." (p. 7-26)

- The 1982 and 1989 Surgeon General's Reports, cited by OEHHA, do not even mention nasal sinus cancer in their discussions of ETS.

OEHHA Claim: "Existing studies consistently show a significant positive association between exposure to ETS and nasal sinus cancer in nonsmokers." (p. 7-28)

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Response:

- ***Lack of Statistical Significance:*** Only one of the risk estimates cited by OEHHA in its discussion of the studies has a confidence interval that excludes 1.0. The single risk estimate that is "statistically significant" has an extremely wide confidence interval, based as it is on only nine cases.

- In Table 7.8 (p. 7-65), OEHHA lists the reported risk estimates from the three nasal sinus cancer studies. The table clearly shows that ***only one of the reported risk estimates has a confidence interval that excludes 1.0.***

- None of the three spousal smoking risk estimates cited by OEHHA from the Hirayama study is statistically significant -- all the confidence intervals ***include*** 1.0. Thus, those risk estimates are consistent with neither an increase or a decrease in risk.

- Fukuda and Shibata do not even discuss the statistical significance of the individual risk estimates in their paper, but OEHHA has calculated confidence intervals. The great width (1.7 to 19.4) of the CI on the risk estimate for more than one smoker in the home illustrates the uncertainty associated with that risk estimate. When coupled with the fact that it is based on only nine cases, this makes any interpretation based on that number highly suspect.

- The authors of the Zheng, et al., study provide only limited information on the spousal smoking analysis. Moreover, the confidence intervals for both risk estimates presented

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overlap 1.0 and are quite wide (as the authors themselves acknowledge), particularly the one for maxillary sinus cancers.

- ***Sample Size:*** OEHHA's conclusion of causality is based on three studies reporting data based on only 91 cases in total. Neither the number of studies nor the number of cases is sufficient support for such a conclusion.

- OEHHA even notes that the Hirayama (1983) study results are based on only 28 cases, but fails to point out that such a small sample size compromises the interpretation of the reported results. The low number of subjects results in very unstable risk estimates.

- Fukuda and Shibata (1990) acknowledge that their data set was of "relatively small size." However, OEHHA's discussion of this study obscures the fact that there are only 35 nonsmoking cases. OEHHA focuses on the risk estimates by exposure category and the purportedly statistically significant "trend," while failing to acknowledge the fragility of those risk estimates, based as they are on 15 and nine cases, respectively.

- While the Zheng, et al., study is fairly large (particularly given the rarity of this tumor), the risk estimates reported for spousal smoking are based on only 28 cases (those who were nonsmokers). Again, sample size is a distinct limitation of this study, a point which OEHHA fails to clearly state in their summary of the paper.

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OEHHA Claim: "The results have been observed in studies . . . with some adjustment for potential confounders." (p. 7-28)

Response:

- OEHHA states that the risk estimates from the Hirayama study included an adjustment for ***husband's*** age. Hirayama has adopted this approach consistently in his analyses of data from this study, when, as it has been noted elsewhere, "[i]t is absolutely routine in epidemiology to standardize for the age of the ***subject***." [emphasis added] (Lee, 1992) Hirayama's odd approach would seem to raise questions about the overall validity of his study.

- Cancer of the paranasal sinuses is more common in Japan than in the United States. (DeVita, et al., 1993; for references to materials not cited by OEHHA, see **Attachment A**) This would imply that caution is warranted in applying the reported results of the Hirayama study (as well as the Fukuda and Shibata study) to the United States population. There may well be ethnic-specific and lifestyle risk factors that have not been considered, as have been reported for nasopharyngeal cancer. (Schottenfeld and Fraumeni, 1996)

- While Hirayama writes in the paper cited by OEHHA that "[n]o other risk factors studied significantly altered the risk of nasal sinus cancer in women," he fails to provide the reader with information as to what those risk factors might be. (Hirayama, 1983) Possible risk factors for this cancer have been called "multifold," and reportedly include exposure to

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nickel; occupation in the furniture, textile, and shoe industries; occupational exposures to chromium, mustard gas, isopropyl alcohol, and radium; and possibly chronic sinusitis. (DeVita, et al., 1993)

OEHHA Claim: "The results have been observed in studies conducted in eastern and western countries, in males and females . . ." (p. 7-28)

Response:

- OEHHA's statement misrepresents the available data, reported for only one sex in each of two countries.

- Two studies present data for nonsmoking ***Japanese women*** (Hirayama; Fukuda and Shibata) and one for nonsmoking ***white American men*** (Zheng, et al.). The Japanese studies do not have data on nonsmoking men, and the U.S. study does not have data on women.

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Section 7.4.1. -- Cervical Cancer

OEHHA Claim: Cervical cancer is listed under "effects with suggestive evidence of a causal association with ETS exposure" in Table ES.1. (p. ES-2)

Response:

- Nowhere does OEHHA indicate how it reached a conclusion of "suggestive" evidence for "causality." In fact, OEHHA's statements in the text of the document do not even mention a causal relationship.

- The Table ES.1 conclusion is not justified or supported by the analysis presented in Chapter 7, which only states: "There is supportive evidence from epidemiological and biochemical studies implicating a role for ETS exposure in the etiology of cervical cancer in nonsmokers." (p. 7-32) OEHHA presents no criteria for extrapolating from this position to a conclusion that there is "suggestive" evidence for "causality," nor does it define what exactly constitutes "supportive" evidence or "suggestive" evidence.

- The reader of the OEHHA document is led to assume that the conclusion of "suggestive" evidence for "causality" is scientifically justified -- because it appears in the Executive Summary of the document -- when, in actuality, OEHHA provides ***no*** rationale at all for such a conclusion, and when the Executive Summary states a conclusion different from the conclusions stated in the text of Chapter 7.

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- OEHHA should formally indicate how it reached the determination of "suggestive" evidence for causality that warranted the inclusion of cervical cancer in Table ES.1.

- OEHHA states in Chapter 7: "[H]uman papillomarivus [sic] . . . has been accepted as the sexually transmitted etiological factor in cervical cancer." (p. 7-28) OEHHA thereby seemingly acknowledges the scientific consensus on the importance of the sexually-transmitted agent, human papillomavirus (HPV), in the etiology of cervical cancer. (See **Attachment A**: Winklestein, 1990; Bosch, et al., 1995; Munoz, et al., 1996; Bosch, et al., 1996) In fact, a consensus panel of the National Institutes of Health has concluded that cervical cancer is "causally related" to infection with HPV. (McNeil, 1996)

- Given the general acknowledgment of HPV as a cause of cervical cancer, it is curious that OEHHA would even evaluate ETS exposure in terms of "causality," as indicated in Table ES.1.

- Moreover, a noted cancer textbook refers to active smoking as a "cofactor" for cervical cancer (DeVita, et al., 1993); given this position, it clearly seems very premature to conclude that there is suggestive evidence that ETS is ***causally*** associated with this disease, as OEHHA claims.

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OEHHA Claim: "The relationship between ETS exposure and cervical cancer was investigated in one cohort and three case-control studies." (p. 7-29)

Response:

- OEHHA's review of the literature on ETS exposure and cervical cancer is incomplete. When additional studies are taken into account, however, no clear picture of "risk" emerges. What seems most likely, based upon the data from these and other studies, is that ETS exposure is a marker for a number of interrelated factors, and that the reportedly elevated risk estimates represent the residual effect of insufficient control for these variables.

- Munoz, et al. (1996), report cervical cancer risk estimates for husband's smoking status that are not statistically significant when adjusted for a number of potential confounding factors. OEHHA did not reference this article.

- Bosch, et al. (1996), report statistically significant cervical cancer risk estimates for husband's smoking, but conclude that the "two most likely reasons" for their reported results are misclassification of human papillomavirus exposure and insufficient adjustment. OEHHA did not reference this article.

OEHHA Claim: "Positive associations were observed in two of three case-control studies and a statistically nonsignificant positive association was observed in the only cohort study conducted." (p. ES-7)

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Response:

- ***Misleading Presentation of Data:*** Table 7.9 (p. 7-66) is incomplete, reporting data from only two of the available studies (Slattery, et al.; Coker, et al.). Nevertheless, Table 7.9 (p.7-66) clearly shows that ***only one cited risk estimate from the two studies is statistically significant.*** Chance has thus not been excluded as an explanation for the overwhelming majority of the reportedly increased risks cited by OEHHA in that table.

- The series of risk estimates OEHHA chose to include in Table 7.9 (p. 7-66) includes the largest risk estimate reported by Slattery, et al., for nonsmokers. The only statistically significant risk estimates for ETS exposure reported in Table 6 of the Slattery, et al., paper are for the highest exposure group for "all" reported ETS exposure or for home ETS exposure. This pattern would be consistent with confounding factors being clustered in that exposure group.

- ***Sample Size:*** It is also clear from Table 7.9 (p. 7-66) that the risk estimates for different ETS "exposure levels" are highly suspect, based as they are on very few cases.

- Moreover, the Slattery, et al., study, which seems to be key to OEHHA's contentions, fails to even provide the numbers of cases and controls for the different levels. This incomplete reporting makes interpretation of the study's reported results quite difficult.

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OEHHA Claim: "There is supportive evidence from epidemiological . . . studies implicating a role for ETS exposure in the etiology of cervical cancer in nonsmokers." (p. 7-32)

Response:

- Many questions remain about the ETS-cervical cancer epidemiologic studies cited by OEHHA, making any summary interpretation of their reported conclusions difficult. Many of the reported risk estimates are not statistically significant. The studies have generally (in some cases, completely) failed to adequately consider potential confounding factors. Given these limitations, OEHHA's conclusion is unwarranted.

OEHHA Claim: "The current chapter extends or modifies the discussion of issues related to ETS exposure and cervical cancer (*e.g.*, on confounders in epidemiological studies . . .)" (p. iii)

Response:

- Compared to the cervical cancer section in the May 1994 External Review Draft, the current Chapter 7 does include some "modified" discussion of confounders, in that they are now briefly mentioned in the context of the data collected in the epidemiologic studies cited by OEHHA.

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- However, OEHHA's treatment of confounders can certainly be further "extended." This is perhaps the most important issue in evaluating the cervical cancer studies. and OEHHA pays completely insufficient attention to it.

- ***Inadequate Treatment of Confounders in Individual Studies:*** The discussion in Chapter 7, plus statements from other reviews, clearly indicates shortcomings in the available literature's treatment of confounding factors.

- It has been stated about the Hirayama study:

> [T]here are a number of doubts about the results from this large prospective study, the most important of which appear to be incompleteness of follow-up and doubts about the validity of the statistical methods used. ***Failure to gather data on confounding variables relevant to specific cancers is also a problem.*** [emphasis added] (Lee, 1992)

OEHHA even acknowledges that Hirayama's ETS data "were not adjusted for potential confounders including subjects' or husband's sexual activity" (p. 7-29). Given what is now known about the relationship between HPV and cervical cancer, this failure on Hirayama's part means that this study can be treated as providing essentially no information relevant to the question of ETS exposure and cervical cancer risk.

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- With respect to the Sandler, et al., study, Lee (1992) notes:

> Apart from . . . the problems of multiple testing, it should be realized that the Sandler I study collected ***no data*** on sexual habits, which are strongly correlated both with risk of cervix cancer and with smoking habits. [emphasis added]

OEHHA acknowledges this as well: "[I]nformation typically obtained in studies of a specific cancer site (*e.g.*, sexual activity in studies of cervical cancer) ***was not collected.***" [emphasis added] (p. 7-29) As with the Hirayama study, the Sandler study can be given little weight in analyses of cervical cancer claims.

- Studies report that both personal smoking behavior and ETS exposure are correlated with a number of other lifestyle factors (related to sexual activity and alcohol and drug use) that appear to be markers for an increased risk of HPV infection. Disentangling the possible effects of these potential confounders is difficult, and the epidemiologic studies to date have not adequately addressed them.

- In a letter to the editor on the Slattery, et al., study, Zang, et al., note:

> In this report, there clearly is undermatching of control patients with regard to important risk factors including sexual activity, religious background, and education. . . . Since the previously mentioned risk factors are correlated highly with one another as well as with active and passive smoking, the risk estimates relating smoking and cervical cancer may be subject to substantial bias and confounding. . . . The effect of adjustment on odds ratios is far greater than expected in case-control studies of this sort, as, for example, the decrease from 14.84 to 2.96 for passive smoke exposure. ***In fact, the adjusted odds***

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> ***ratios are probably no more than the leftover effect of variables controlled imperfectly by logistic regression.*** [emphasis added]

- Zang, et al., also note:

> The apparent association between cervical cancer and environmental smoke exposure may, in fact, be the result of increased exposure to papillomaviruses or herpes simplex virus 2 through contact with male sexual partners who smoke, since one might expect smokers to be generally more sexually active than nonsmokers, and case patients are more sexually active than control subjects.

- The author of a 1992 book on ETS chronic disease claims stated about the Slattery, et al., study:

> [T]he major problem with interpreting this finding as cause and effect is the extreme difficulty of adequately adjusting for sexual habits. . . . Since the number of sexual partners is only an inaccurately measured surrogate of the true sexually related cause of cervix cancer . . . the adjustment will be incomplete and leave a residual confounding effect. ***It is entirely plausible that the whole of the adjusted relative risk could be explained by this.*** [emphasis added] (Lee, 1992)

- That potentially misleading results can come from studies with inadequate attention to confounding factors (e.g., Hirayama, as acknowledged by OEHHA; Slattery, as pointed out by other reviewers) seems clear when the Coker, et al. (1992), study is compared to those other studies. In that study, the authors included age, race, education, number of Pap smears, number of sexual partners, and history of genital warts as confounders in their analysis of ETS exposure and cervical cancer risk. As for their reported results, they note, "the

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confidence intervals associated with each of these adjusted odds ratios were ***wide and clearly not statistically significant.***" [emphasis added]

- ***Omission of Relevant Data:*** In the discussion of cervical cancer, OEHHA completely overlooked two articles presenting relevant data on the potential for confounding in the epidemiologic studies. Given OEHHA's predilection for data from California elsewhere in the report, this omission seems particularly odd.

- Holly, et al. (1992), report data which "confirm that cigarette smoking is strongly associated with numerous life-style and behavioral factors, many of which have been linked directly or indirectly with cervical cancer." These data were collected from women residing in the San Francisco Bay area.

- In another study from the same research group, Cress, et al. (1994), investigated whether women exposed to ETS differed from non-exposed women on a number of characteristics. This study was based on self-report of ETS exposure, just as are the epidemiologic studies of cervical cancer risk. Several statistically significant differences between "ETS-exposed" and non-exposed women were reported; they included marijuana use, beer consumption, and being divorced or separated. The authors concluded:

> [W]omen nonsmokers exposed to passive smoke were different from those not exposed. Studies that examine the association between passive smoking and disease need to measure dietary, lifestyle,

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sexual, and reproductive factors to adequately allow for these differences.

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